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The effect of low dose lofepramine in depressed elderly patients in general medical wards

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1 A double-blind randomised controlled trial of the effect of low dose lofepramine (70 mg once daily) against placebo was carried out on depressed elderly inpatients on general medical wards for the elderly, comparing measures of depression and side-effects between the randomised groups. Patients were identified for the study using the Geriatric Depression Scale (GDS) and the Brief Assessment Schedule Depression Cards (BASDEC).

2 Sixty-three subjects were randomised: 46 patients completed the entire trial of 28 days treatment. BASDEC and GDS were administered on day 8 post-admission, and depressed patients were randomised double-blind to either low dose lofepramine (70 mg daily) (n = 23) or placebo (n = 23). Assessment of changes in depressive states were made using the Montgomery Asberg Depression Rating Scale (MADRS) on days 8, 18 and 36 post-admission.

3 Both groups improved by a similar amount during the trial. Lofepramine tended to be more effective than placebo in those patients who were more depressed (GDS $\geqslant$ 18). On the other hand, subjects who were less depressed (i.e. GDS $<$ 18) improved more on placebo than lofepramine.

4 Low dose lofepramine may prove useful in moderately or severely depressed patients treated for only 4 weeks. However, low dose lofepramine is not indicated for mild (GDS 15–18) depression.

Keywords lofepramine depression elderly

Introduction

Depressive symptoms, akin to sadness, are frequently experienced by elderly hospitalised patients. Studies indicate a prevalence of between 5–30% [1]. However, the boundaries between normal sadness and pathological depressive illness are often blurred. In view of this dilemma, several depression scales have been designed to evaluate better the range of affective phenomena which constitute clinical depressive illness. An important modality of treatment for both depressive symptoms and illness is with antidepressants. Unfortunately, some antidepressants in conventional doses may produce confusion and adverse interactions with other drugs, especially in the elderly. Many physicians adopt the practice of prescribing half, or even a third, of the conventional dose in the elderly without established scientific basis. Indeed, pharmacodynamic studies on healthy elderly patients given a single daily low dose of lofepramine (70 mg) have demonstrated that 'conventional therapeutic levels' are not reached [2]. For these reasons we decided to test the efficacy of low dose lofepramine (70 mg daily, which is a third to half the recommended dose) over 4 weeks. Lofepramine was chosen in preference to other tricyclic drugs because it may be as efficacious as the older tricyclics [3] and has less severe side-effects [4, 5]. Elderly patients often have multisystem disease and lofepramine was thought to be most appropriate because

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of its wider safety margin, both in clinical use and overdosage [6]. This study was carried out in medical rather than psychiatric wards.

Methods

Study subjects were elderly (above 65 years old) inpatients chiefly from the wards of the Division of Geriatric Medicine, Hammersmith Hospital, with some patients from the general wards at St Charles' Hospital. Recruitment of patients took place from April 1989 to October 1991. On admission, patients had cognitive function evaluated by an Abbreviated Mental Test Score (AMT) [7]. Those patients assessed as having either normal or only mildly impaired cognitive function (AMT > 7/10) were then screened for depression 7 days after admission. Apart from dementia, criteria for exclusion from the study included life-threatening illness, pre-existing antidepressant therapy and any specific medical contraindications such as a history of dysrhythmias, urinary retention, glaucoma and previous allergies. Suicidal patients were also excluded for ethical reasons. The 7 day delay was to initiate treatment for acute illnesses (which may either mask or mimic depression [8]) and to allow the patients to become accustomed to their surroundings. Screening involved the use of Brief Assessment Schedule Depression Cards (BASDEC) [9] and the Geriatric Depression Scale (GDS) [10]. BASDEC is a novel 19 card screening programme designed for ease of administration in the ward setting which has been found to correlate well with the GDS. Patients with GDS $\geqslant$ 15/30 were entered into the study, $\geqslant$ 15 being the recommended cut-off point for depression. Alternatively, the threshold score for entry was greater or equal to 6/21 on BASDEC. Study subjects were then graded by the Montgomery Asberg Depression Rating Scale (MADRS) [11] as this is sensitive to the effects of drug treatment. The study objectives were explained to the patients and written consent obtained from participants. The study was approved by the local ethics committees of both Hammersmith and St Charles' Hospitals.

Study subjects were assigned to placebo or lofepramine by double-blind randomisation, identical capsules being used for each treatment. After 10 and then 28 days (i.e. 18 and 36 days post-admission respectively), patients were reassessed by the same examiner using MADRS. Blood pressure, pulse, liver function blood tests as well as electrocardiograms were repeated on these occasions for objective evidence of side-effects, and patients were asked standard questions about the common side-effects of dry mouth, blurred vision and day time drowsiness. General practitioners of the patients were informed of inclusion into the trial, lest drugs which may interact with the trial drug were prescribed after discharge. Patients discharged before the 36 day period were given follow-up appointments or visited at home if they were unable to attend an outpatient clinic. At the end of the trial, patients were referred to the psychiatrist if they were judged to be clinically depressed.

The Wilcoxon rank sum test was used for testing the difference between the two treatment groups. The confidence interval for the mean change was based on the *t*-distribution and Fisher's exact Chi-square test for two-way tables. Analysis of covariance was used to analyse the changes in liver function tests (i.e. alkaline phosphatase and aspartate transaminase). Patients were also categorised according to severity of depression by GDS at entry to the trial, into two groups above and below median score.

Results

Sixty-three patients were randomised (31 to placebo, 32 to lofepramine), equal numbers of patients on placebo and lofepramine completed the full 36 day trial (23 in each group) and 17 (27%) did not. There were two deaths, one in each treatment group, which were due to cardiac congestive failure and chest infection unrelated to the trial medication. The other reasons for non-completion were patient non-compliance ($n = 2$), missed appointments ($n = 4$), patient withdrawn ($n = 4$), and unknown ($n = 5$). Thirty-six percent of patients randomised to placebo were prescribed an antidepressant at the end of the trial, compared with 27% patients randomised to lofepramine ($P = 0.5$).

The characteristics at baseline are given in Table 1. With one exception, there was no significant difference in any entry variable between the two groups. Pretreatment, the mean alkaline phosphatase was higher in the placebo group because an individual in this group had concomitant Pagetic bone disease and a value of 601 iu l^{-1}.

Table 2 gives the change in MADRS score according to treatment group as well as the initial GDS rating for

Table 1 Characteristics (mean ± s.d.) of the two treatment groups at entry

	Placebo	*Lofepramine*
n	31	32
% male	23%	44%
Age	80 (6.0)	80 (7.9)
Systolic blood pressure (mm Hg)	137 (18.0)	138 (22.1)
Diastolic blood pressure (mm Hg)	77 (8.7)	80 (11.1)
Pulse rate	76 (12.0)	85 (21.0)
Alkaline phosphatase (iu l^{-1}) [median]	208 (140.3) [146]	134 (68.8)* [117]
Aspartate transaminase (iu l^{-1}) [median]	46 (46.5) [27]	33 (21.1) [27]
% with no psychiatric history	77% ($n = 31$)	83% ($n = 29$)
BASDEC [median]	10.8 (2.7) [10]	11.0 (3.8) [10]
Geriatric depression scale [median]	16.6 (3.3) [17]	17.0 (4.3) [17]
Montgomery Asberg depression rating scale [median]	17.8 (5.3) [18]	17.0 (7.4) [16]

Significance of between group differences: * $P < 0.05$.

Table 2 Change in Montgomery Asberg depression rating scale (MADRS) by treatment group and according to initial geriatric depression scale (GDS) rating

	Placebo (P)			*Lofepramine (L)*				
	n	*Mean (s.d.)*	*Median*	n	*Mean (s.d.)*	*Median*	*95% CI for P-L*	P
Change after 10 days								
Initial GDS < 18	17	+5.2 (4.4)	+5.0	16	+3.8 (4.3)	+3.0	(−1.6, +4.5)	$P = 0.2$
⩾ 18	12	+6.1 (4.5)	+5.5	10	+8.6 (10.2)	+8.5	(−9.3, + 4.2)	$P = 0.6$
Total group	29	+5.6 (4.4)	+5.0	26	+5.6 (7.4)	+3.5	(−3.0, +3.0)	$P = 0.5$
Change after 28 days								
Initial GDS < 18	14	+7.9 (4.9)	+8.0	14	+3.7 (4.7)	+4.0	(+0.4, +7.9)	$P = 0.04$
⩾ 18	9	+8.9 (7.7)	+6.0	9	+15.9 (8.2)	+16.0	(−14.9, +0.9)	$P = 0.07$
Total group	23	+8.3 (6.0)	+8.0	23	+8.5 (8.6)	+7.0	(−4.6, +4.2)	$P = 0.8$
Change after randomisation Intention-to-treat analysis								
Initial GDS < 18	17	+7.2 (5.2)	+8.0	16	+3.8 (4.7)	+4.0	(−0.1, +7.0)	$P = 0.06$
⩾ 18	12	+7.7 (7.3)	+6.0	11	+12.6 (10.5)	+13	(−11.3, +1.3)	$P = 0.2$
Total group	29	+7.4 (6.1)	+6.0	27	+7.4 (8.6)	+6.0	(−4.0, +4.0)	$P = 0.6$

A positive change implies an improvement.

Table 3 Reporting of symptoms at baseline and at the end of the study (intention-to-treat analysis)

	Placebo % complaining			*Lofepramine % complaining*		
	n	*Baseline*	*End of study*	n	*Baseline*	*End of study*
Dry mouth	28	46%	61%	24	46%	67%
Blurred vision	27	15%	15%	23	30%	26%
Drowsiness	27	37%	33%	24	33%	33%
Abnormal bowel habit	28	39%	36%	25	44%	52%
Difficulties with micturition	28	21%	21%	26	19%	15%
Capsules disagreed with patient at any time	26	—	31%	26	—	38%

the 55 patients who completed 10 days treatment, the 46 patients who completed 28 days and the 56 patients with outcome data after randomisation (an intention-to-treat analysis). There was no significant difference in the change in MADRS scores between the two treatment groups. The mean improvement in MADRS of the lofepramine group was almost identical to that on placebo. However, in patients who were more depressed (i.e. GDS ⩾ 18), low dose lofepramine tended to improve depression scores more than placebo at the end of the 28 day treatment period. The difference in the mean change in MADRS between placebo and lofepramine was −7.0 ($P = 0.07$; 95% CI −14.9, +0.9). On the other hand, subjects who were less depressed (i.e. GDS < 18) improved more on placebo than lofepramine, the difference in the mean change in MADRS between placebo and lofepramine being +4.2 ($P < 0.05$; 95% CI +0.4, +7.9).

With respect to objective side-effects, it was noted that there was a slight decrease in the mean pulse rate at the end of treatment compared with the baseline (1.5 beats min^{-1}). Electrocardiograms (ECGs) done at the end of treatment were also compared with baseline ECGs, and there were no cases where a change from normal to abnormal was reported. In our study, after 10 as well as 28 days of treatment, alkaline phosphatase was raised in some patients treated with low dose lofepramine, but the differences were not found to be significant.

Table 3 gives the reporting of side-effects. These depressed patients had several complaints both at the beginning and the end of study period.

We compared symptoms at baseline and at the end of the study and made intention-to-treat analysis. We found that overall, 38% of patients said that low dose lofepramine disagreed with them, as compared with 31% of those on placebo. Slightly more patients on low

dose lofepramine complained of abnormal bowel habits, 52% and blurred vision, 26%. This contrasted with 36% and 15% respectively, for those on placebo.

Discussion

The treatment of depression remains a complex issue, especially in the elderly, and treatment is often supportive rather than curative. There is a spectrum of depression to be treated, from depressive symptoms to depressive illness, and making this distinction may make treatment more appropriate. A wide range of therapeutic measures including non-drug treatment such as sunlight has been suggested [12]. The underlying mechanism of depression may be related to changes to central concentration of neurotransmitters, and antidepressants are believed to act by altering neurotransmitter levels. In this study, we wished to assess the efficacy of single dose (70 mg) of lofepramine, having made the assumption that biological half-life and therapeutic half-life of the drug could be different. This drug is normally prescribed in a dose of 70 mg two to three times daily, but lower doses may be preferable. Dorman [6] has suggested that in a proportion of elderly patients, 70 mg at night may be effective.

This study showed that for all grades of depression, low dose lofepramine was no more effective than placebo at the end of 28 days' treatment (mean change in MADRS score of 8.48 compared with 8.26 respectively). A possible explanation for the lack of difference is that in both groups, the overriding factor was an improvement in their physical condition and a possible benefit from sympathetic attention to their depression. Alternatively, it is possible that elderly patients are over-enthusiastic when reporting symptom improvement, not wanting to disappoint the interviewers. This may account for mildly depressed patients (GDS < 18) showing an improvment on placebo.

According to the work done by Yesavage & Brink [10], patients are classified as mildly depressed when the GDS is between 15 to 22, and severely depressed when the GDS is more than 23. We found that after 28 days treatment, patients with GDS $\geqslant 18$ (i.e. who were moderately depressed) tended to have a better response in mood elevation on low dose lofepramine than placebo ($P = 0.07$). It may be that low dose lofepramine was more effective than placebo in this group because we are treating depressive illness rather than depressive symptoms. This is implied, as on the whole, depressive illness would score higher on depression ratings (i.e. GDS or BASDEC).

The safety of low dose lofepramine was reinforced in this study [3, 5]. Although there have been case reports of abnormal liver function tests following treatment with lofepramine [13], in our study using low dose lofepramine the elevation of liver enzymes compared with patients on placebo was not significant. There were also no significant changes in heart rates nor electrocardiograms, supporting previous work done on the cardiac safety of lofepramine [3].

Is low dose lofepramine (70 mg daily) as effective as conventional daily doses of 140–210 mg in elderly patients with moderate or severe depression? This trial did not support the use of low dose lofepramine in elderly patients with mild depression (GDS 15–18). This suggests that low dose lofepramine may not be effective for depressive symptoms *per se*. A low dose is probably safer for elderly patients but one has to balance efficacy with safety. A comparative trial in patients with moderate to severe depression/depressive illness is required to answer this question.

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